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13. ABSTRACT

The symposium is composed of two articles, one on the history of fevers of undetermined origin in American soldiers in Vietnam and another on malaria. Malaria is recognized as the return of old problem to the American physician since the rotation of American soldiers from Vietnam has brought it again into the Continental United States. In the middle portion of the journal (68 pages), there is a group of capsule summaries - the potential medical problems in returning American prisoners of war from Southeast Asia. Each summary is an outline (symptoms, signs, diagnosis, treatment) placed on a separate page. The diseases commonly seen in the United States to which these men may also have been subject (e.g. hepatitis, hypertension, arteriosclerotic heart disease) are not included.

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PRESENT CONCEPTS

IN INTERNAL MEDICINE

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Recent Concepts, Vol V, Supplement 1, 1972

ii

PRESENT CONCEPTS IN INTERNAL MEDICINE
VOLUME V 1972 Supplement 1

MEDICAL DISEASES OF MILITARY SIGNIFICANCE Southeast Asia 1972

CONTENTS

Department of Medicine
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SYMPOSIA 1972

PRESENT CONCEPTS IN INTERNAL MEDICINE
Volume V, Numbers 1 through 6

MONTH	SYMPOSIUM
January	Gastroenterology, Part I
February	Gastroenterology, Part II
March	Gastroenterology, Part III
April	Major Metabolic Diseases
May	Cardiology
June	Pulmonary

FOREWORD

A chapter in the history of the Medical Corps, United States Armed Forces, is rapidly drawing to a close. The era of massive troop exposure to the hazards of the Southeast Asian environs is over. One major challenge remains — the medical rehabilitation of returning Americans who have been prisoners of war.

It is therefore appropriate to dedicate an issue of *Present Concepts in Internal Medicine* to an updating of some of the lessons learned by the Medical Corps throughout the Southeast Asian Conflict. Colonel John J. Deller, Jr., MC, is a major contributor to the early understanding of the vexing problem of fevers of undetermined origin among combat troops in Vietnam, and has contributed to the training of many Medical Officers in the recognition and treatment of these diseases. In the first article of this issue, he shares with us a historical perspective of the development of the Medical Corps' expertise in this area. This treatise will be a part of a volume entitled *History of Internal Medicine, Vietnam*, Office of the Surgeon General, Department of the Army.

In addition to the acute febrile diseases encountered by a temporary sojourn in South Vietnam, returning prisoners of war may evidence morbidity from dietary deficiencies, and diseases peculiar to North Vietnam. A survey of these problems, presented in reference-manual style, is the second article.

Malaria emerged not only as the most serious acute febrile disease encountered throughout the years of conflict, but also as a significant cause of disease among Vietnam veterans returning to the United States. A paper on this subject, which originally accompanied a scientific exhibit appearing at several national conventions, has been updated and is included in this issue.

MAJ Carl C. Peck, MC
Guest Editor

HISTORY OF FEVERS OF UNDETERMINED ORIGIN IN AMERICAN SOLDIERS IN VIETNAM

COL John J. Deller, Jr., MC

Historical Comments

In a span of fifty years, the United States has been engaged in four major wars. Despite the trend of history and the lessons learned, people tend to forget the knowledge gained from wars past -- perhaps that is why wars continue to happen. Likewise, we tend to forget from one war to the next the knowledge gained in military medicine. Each war has called upon a new generation of physicians to solve the medical problems of American soldiers. The medical officers in the mid-1960s were as ill-prepared to identify and treat the diseases acquired by the American servicemen in Vietnam as were the generations before them. The majority of the physicians assigned in Vietnam had only skimmed the textbook chapters in tropical disease and, I dare say, had never removed the archives of medical history from World War I or World War II from their dusty shelves. Tropical disease was not a popular subject in American medicine; its scholars were few and, for the most part, they belonged to an earlier generation. Even within the military service only a few scholars of this field remained.* If it had not been for their foresight and guidance, we would surely have floundered during the early days of the Vietnam War.

*Several of the notable physician-scholars were General James E. Weir, MC, General William D. Tigertt, MC, General Robert E. Blount, Sr., MC, Colonel Thomas W. Sheehy, MC, and C.J.D. Zarafonetis, MD.

Unfamiliarity with Tropical Medicine

The problem of "fevers of undetermined origin" (FUO) was perhaps one of the greatest diagnostic dilemmas for military physicians in Vietnam. Historically, the "FUO" problem in Vietnam in the mid- 1960s was not very different from the FUO problem during World War II. At one time during the Pacific campaign there had been so many such diagnoses that Colonel Henry M. Thomas (Consultant in Medicine, Southwest Pacific Area, 1943) was given special instructions to investigate the matter. Every case he observed, he agreed, the diagnosis was indeed in real doubt — it was an FUO. The problem was so acute that it prompted him to prepare a compilation on the differential diagnosis of these acute fevers. (Technical Memorandum No. 7, Office of the Chief Surgeon, Headquarters, USASOS, 21 March 1944) /1/ Despite the magnitude of the problem, however, no comprehensive FUO studies are recorded in the medical history of World War II. Several studies attempting to clarify the FUO problem when it emerged in Vietnam were conducted. It is primarily from these studies and other related published reports that this review of the history of fevers of unknown origin in American soldiers during the Vietnam War is written.

Incidence/Epidemiology

The first available statistics on the magnitude of the FUO problem stem from the AMEDS Activity Reports beginning in October 1965. During the last three months of that calendar year, disposition diagnoses reported from three major hospitals in Vietnam (Third Field, Eighth Field, and 85th Evacuation) reported 479 FUO cases. The average duration of hospitalization for this group was seven days. AMEDS Activity Reports continued to show that FUOs constituted a major cause of hospitalization among American troops in the Republic of Vietnam through 1970. During the period from 1966 through 1969, the total FUO problem (as reflected in monthly morbidity reports) revealed an average incidence rate of 58 per 1,000 strength per year (range from 35 to 100 per 1,000). These figures include nonhospitalized patients receiving Division-level medical care as well as those treated in field and evacuation hospitals. In comparison with other common diseases, the diagnosis of FUO ranked second only to venereal disease, common respiratory disease, diarrheal diseases, skin diseases, and malaria all ranked lower. The average duty time lost because of FUOs (reports from all sources) during the period 1965 through 1970 was 4.5 days. It has been emphasized that the monthly incidence rate, as reflected from morbidity reports, may be inflated because a number of ill-defined conditions were

reported as FUOs and some cases initially reported as such were not changed after a more definitive diagnosis was established. /2/ Nevertheless, fevers of undetermined origin constituted one of the major causes of man-days lost during the Vietnam War.

The distribution of FUOs by type of unit (as classified by amount of field exposure) revealed that combat troops have significantly more cases (greater than 400 percent) than do support troops (60 percent) and rear support troops (20 percent). /2/ This distribution fits with the expected exposure to arthropod vectors and the other environmental conditions conducive to development of tropical febrile diseases. In the first analysis which was made of the fevers of unknown origin in American soldiers in Vietnam, Deller and Russell /3/ found that a history of the soldier's activity, i.e. whether he had been in actual combat and exposed to the jungle or whether he had been in a support unit at a large encampment, provided key information in separating the various causes of FUO. For example, the arboviral diseases and murine typhus occurred most frequently in areas of large population density because such areas were natural habitat of the vectors, whereas malaria and scrub typhus were contracted only when the natural habitat of their vectors (heavily forested and jungle areas) were invaded.

Hinderances to Early Specific Diagnoses

One of the major hinderances to defining the spectrum of tropical febrile diseases in the early years of the war was the lag in obtaining adequate laboratory support. Although most hospitals arrived in RVN with a full complement of personnel, the pathologists, bacteriologists, and laboratory technicians were as unfamiliar with tropical disease as the clinical personnel. However, more importantly, they did not have the equipment to accomplish the sophisticated laboratory procedures necessary to support "tropical disease hospitals". It was only through the United States Army Medical Research team in Saigon and their close working relationship with the SEATO Laboratory in Bangkok that early studies were at all possible. It was not until 1968 that a full laboratory capability was established in the Republic of Vietnam for the sole purpose of supporting infectious disease problems, *i.e.* the Ninth Medical Laboratory established a separate department of infectious disease and made available multiple screening procedures for the sero-diagnosis of FUOs.

Although world health surveys of major disease prevalence had been conducted in the early 1950s in Vietnam /4,5/, these data were incomplete for the needs of the American soldier and physicians in South

Vietnam. Nevertheless, they did provide a beginning. By analyzing the surveys, coupled with reports from the French Indochina experience and from the archives of the Pasteur Institute in Saigon, one could predict potential tropical disease problems. Table 1 lists some of the acute febrile diseases which one might have expected to encounter in Southeast Asia. It will be seen from the review which follows that such a probability table serves as a useful guide.

TABLE 1

PROBABILITY OF ACUTE FEBRILE DISEASE ACQUISITION BY AMERICAN SOLDIERS IN REPUBLIC OF VIETNAM

DISEASES NOT PRESENT IN VIETNAM	DISEASES PRESENT BUT IMMUNIZATION GIVEN/AVAILABLE	DISEASES PRESENT AND LIKELY TO BE ACQUIRED
Viral	*Viral*	*Viral*
Yellow fever	Hepatitis	Dengue
Smallpox	(gammaglobulin)	Japanese B encephalitis
Rickettsial		*Rickettsial*
Epidemic typhus		Scrub typhus
Relapsing fever		Murine typhus
Spotted fever		
	Bacterial	*Bacterial*
	Plague	Leptospirosis
	Cholera	Melioidosis
	Typhoid	Tuberculosis
Parasites, systemic		*Parasites, systemic*
Schistosomiasis		Malaria
		Amebic liver disease

CLINICAL STUDIES

The FUO study was written by a number of physicians of various disciplines, and, to my knowledge, not one of them had been in the field

of tropical medicine. These were physicians who were thrown together in a common ground of frustration by the contingencies of war. They were faced with a new chapter in their medical careers -- a chapter that could be entitled "Combat Medicine in the Tropics". It seemed at first that all disease under these circumstances was a "FUO" -- the triad of fever, chills, and headache was so common that on the surface everyone seemed to suffer from the same malady. It became obvious, however, that there was a spectrum of disease within this massive group and that the various diseases could be and must be separated.

What could be done? The first step was to design a study which would survey the possible specific etiologies, prove in the laboratory what each patient actually had, and then attempt to correlate differentiating clinical features to specific disease entities. By so doing, it would then be possible to separate on clinical grounds various specific entities and whittle the number of FUOs to the minimum. This approach was conceived at the 93rd Evacuation Hospital in the spring of 1966. The hospital had just been converted from tents in a recently cut forest to crossed Quonset huts in an area which subsequently has developed into the massive Long Binh USARV military complex. It had a basic laboratory, but our study required more sophisticated laboratory support. The idea of an FUO study was presented to LTC Robert Joy, MC, Commander of the US Army Medical Research team in Saigon. He was most receptive and encouraging and arranged with Major Philip Russell, MC, at the SEATO Laboratory in Bangkok to receive the specimens and do the appropriate diagnostic work. Despite generator-run freezers, makeshift portable dry ice chests, 110 degree weather, unsure jeep transportation to Saigon, and courier airlifts to Bangkok, specimens were collected, stored, and delivered to their destination -- and more importantly, results were returned in record time. It was not long after the first results were returned that our focus began to clear and it was possible to separate many of the FUOs into a limited number of specific diagnoses. Following this initial study /3/, conducted April through August 1966, two subsequent studies /6,7/ were done through the continued support of the United States Army Medical Research team and the SEATO Laboratory. In addition to these Army studies, a study was also conducted by the Navy (1967) /8/ and another by the Air Force (1967-1968) /9/. The combined results of these studies, done over a period of two years (1966 to 1968) and during various seasons and different geographical zones in Vietnam, provide an excellent composite of the total spectrum of FUOs in American servicemen in the Republic of Vietnam.

Spectrum of FUOs

A fever of undetermined origin in the context of this review is defined as a febrile illness which required admission of the patient to a field or evacuation hospital and which could not be more specifically diagnosed during the initial three days of hospitalization. (The definition of an FUO varied in the different studies from "cases not diagnosed within the first 24 hours" to "cases remaining febrile during their hospital stay".) In general, an undiagnosed fever for three days is applicable to all the data. Although each of the five major FUO studies varied somewhat in design, the overall analysis of these studies permits an appraisal of these illnesses which can masquerade initially as FUOs as well as those illnesses which remain as the *truly undiagnosable fevers* (TUF). The results of the five major FUO studies done in the Republic of Vietnam between 1966 and 1968 are presented in Table 2. The Army studies of Deller and Russell /3/, Reiley and Russell /6/, and Colwell et al /7/ were all prospective and comparable in design. The study by Berman et al (USN) /8/ specifically excluded all cases of malaria, whereas Deaton's study (USAF) /9/ was retrospective and included all hospitalized malaria cases. Thus, there are some numerical differences in the non-Army studies compared to the Army studies. It is apparent from review of these data that it is possible to distinguish the specific diagnostic category for nearly three-fourths of all patients initially considered to have a FUO. These fall into five major groups (1) group A and B arboviruses - chikungunya, dengue, Japanese B encephalitis; (2) rickettsial diseases - scrub and murine typhus; (3) leptospirosis; (4) malaria; and (5) miscellaneous.

Table 3 categorizes the miscellaneous group. Within this group, only two major categories represent any significant contribution to the total FUO problem. These were enteric diseases comprising 28 cases of the combined series, and respiratory tract diseases (13 cases) including acute respiratory disease, bacterial pneumonia, and viral pneumonia.

The remaining truly undiagnosable fevers made up from one-fourth to one-half of the cases depending on the completeness of laboratory screening. These cases can generally be separated into two major groups based on the clinical picture: (1) approximately one-half of these cases had clinical features (fever patterns, rash, leukopenia) which suggest an arbovirus or typhus fever;*

*In the Army studies /3,6,7/, the Weil-Felix test was not used to screen for Rickettsial disease, nor was the specific complement fixation test for murine typhus used. Thus, in view of the later studies, a number of the TUFs included in these reports may have been murine typhus.

TABLE 2
RESULTS OF FIVE "FUO" STUDIES IN REPUBLIC OF VIETNAM, 1966-1968

STUDY	LOCATION	YEAR	MONTHS	NUMBER OF CASES	PERCENT SPECIFICALLY DIAGNOSED							
					Malaria	Dengue	Jap B	Chik.	Lepto	Typhus Fevers Scrub	Murine	Other Diagnoses	FUO
Deller, Russell/3/ (Army)	93rd Evac Long Binh	1966	April ↓ August	110	7	28	1	9	1	8	0	17	26
Reiley, Russell/6/ (Army)	8th Field Nha Trang	1966-1967	October ↓ February	93	6 4	10 6	0	(1	11.6	13 8	0	18	38
Colwell et al/7/ (Army)	Dong Tam, Mekong Delta	1967	June ↓ December	87	12 6	11	(1	0	3 4	2.3	0	16	54
Berman et al/8/ (Navy)	I Corps	1967	February ↓ September	295	Excluded by design	3 4	8.1	0	17	14	0	10	51
Deaton/9/ (Air Force) Retrospective	12th USAF	1967-1968	July ↓ June	306	70*	5	0	0	2	1	8	3	12
TOTAL ARMY, NAVY, AIR FORCE				892									181

*All cases admitted as FUO included
Abbreviations: FUO = fevers of undetermined origin, Jap B = Japanese B encephalitis, Lepto = Leptospirosis, Chik. = Chikungunya.

(2) the remaining half were a heterogenous group usually with fevers of less than 72 hours duration and often with upper respiratory or gastrointestinal symptoms. Perhaps of greater significance in an analysis of this group is that all TUFs had self-limited illnesses, thus even if a specific viral or rickettsial etiology was to blame, the outcome was favorable and no major life-threatening illnesses were hidden within this group.

TABLE 3

"MISCELLANEOUS DIAGNOSES RECORDED IN "FUO" STUDIES, VIETNAM 1966-1968

DIAGNOSIS	Deller, Russell/3/	Reiley, Russell/6/	Colwell et al /7/	Berman et al /8/	Deaton/9/	TOTAL
Melioidosis	2	...	...		1	3
Amebiasis	1	3	...	7	3	14
Drug sensitivity	1	..	3	...	...	4
Gonoccal and lower urinary tract infection	3	.	1	...	...	4
Pericarditis	1	1	...	...	...	2
Pneumonia, acute respiratory distress	1	(	6	...	...	13
Shigellosis	4	...	...	...	...	4
Other diarrheas	6	...	...	...	4	10
Encephalitis (nonspecific)	...	2	...	...	...	2
Infectious mononucleosis	..	1	1	4	...	6
Plague	...	1	...	...	...	1
Hepatitis	...	...	3	...	...	3
Others (nonspecific)	...	...	...	...	18	18

CLINICAL FEATURES OF THE MAJOR SPECIFIC TROPICAL DISEASES PRESENTING INITIALLY AS "FUOs"

FUO studies done in RVN served two major purposes: (1) they established the spectrum of tropical febrile disease affecting American soldiers

in different seasons and in different geographical locations throughout South Vietnam, and (2) they clarified a number of important differential diagnostic features of specific illnesses which masquerade as fevers of unknown origin.

The diagnostic features of the major diseases uncovered in these studies will be reviewed in the subsequent pages. Their relative incidences are depicted in Table 2. It is of both historical and practical significance that throughout the period of our highest troop concentrations in Vietnam (1965 through 1970) the same spectrum of diseases was encountered and only the relative frequencies varied. The importance of this knowledge lies not only in its historical value, or in its redefinition of clinical features of a number of tropical diseases, but rather in the direction which it should point our future preventive medicine efforts.

Malaria

Malaria was the tropical disease of greatest concern because it caused the largest number of medical casualties in Vietnam (as well as the largest number of acute febrile diseases imported into this country from RVN). Of the four types of human malaria, fully 99 percent acquired by Americans in Southeast Asia were due to the *Plasmodium falciparum* or the *Plasmodium vivax*, and approximately 90 percent of the cases of malaria diagnosed in the Republic of Vietnam in American soldiers were the result of infection with *P. falciparum*. Thus, in any patient with an FUO, malaria must receive prime consideration.

Malaria is generally easy to diagnose if one examines a peripheral blood smear and knows how to interpret it. Smears, however, do not always reveal parasites at the initial presentation and thus, the diagnosis of "FUO" is recorded when subsequently the condition is proved to be malaria. Since the Anopheles mosquito (the primary vector of malaria) is a jungle breeder, this disease is most suspect in a soldier who has been in combat.

The majority of patients with malaria will have a fever above 104 F within the first 72 hours of illness. Frequently the temperature goes to 105 or 106 F and when temperatures of this elevation are found, the diagnosis is usually malaria. The fever becomes even more discriminating when following a spike the temperature returns to 99 F or lower before the next paroxysmal elevation. Such a pattern is distinctly unusual with the other tropical infections. The shaking chill, the hallmark of malaria, is

generally present and is accompanied by headache, moderately severe myalgias, and a variety of gastrointestinal complaints in the majority of patients. The most remarkable feature about the physical examination is the absence of specific findings, except for percussion tenderness over the liver or spleen, or both, the examination is frequently negative unless the patient has one of the major complications seen with falciparum malaria. Splenomegaly is variable and probably depends on the duration of the subclinical illness before the onset of recognizable disease. Where the diagnosis of malaria is suspect, a series of blood smears, both thick and thin, must be done to confirm it. A Wright-stained thin smear carefully examined is the best way for the physician to make a diagnosis. Thick smears, although providing a faster answer, are better left for the specialist or parasitologist to interpret.

Malaria is perhaps the single most important tropical disease to be separated rapidly from the remainder of the FUOs because its treatment must be timely and the regimen is specific. The treatment of malaria had several changes following the appearance of cholorquine-resistant strains of *P. falciparum* in 1965 in RVN. Despite increasing numbers of multi-drug resistant strains of *P. falciparum* since that time, the available drugs for the treatment of malaria affected a primary cure in 98 percent of the cases. The standard treatment of vivax malaria did not change as the *P. vivax* did not demonstrate any significant resistance to the standard drugs, cholorquine and primaquine. The treatment schedule for *P. vivax* infection remains as follows: choiorquine phosphate, 1.0 gm (600 mg base) followed by 0.5 gm in 6 hours and 0.5 gm daily for 2 days; primaquine, 15 mg base, is given daily for 14 days. Since over 50 percent of *P. falciparum* infections acquired in Vietnam have been resistant to cholorquine, patients with this infection were treated with quinine. Quinine, when used properly, proved to be relatively safe as well as effective, especially when combined with antifols (pyrimethamine and a sulfonamide). "Triple therapy" for falciparum malaria eventually evolved and the treatment schedule which emerged as "standard" includes the following: quinine, 650 mg every 8 hours for 10 to 14 days; pyrimethamine, 25 mg q 12 hours for 3 days; and sulfisoxazole (Gantrisin ®), 500 mg 4 times daily for 7 to 10 days.

It is important to realize that there may be mixed infections, in which case the treatment for falciparum malaria plus the additional therapy for the exoerythrocytic phase of vivax malaria (i.e. primaquine) should be administered. It is also possible that patients with malaria of either type may have another tropical disease simultaneously. In several of the FUO studies, scrub typhus was the other disease most commonly associated with malaria, probably because it is also acquired in the same jungle environment as is malaria.

Dengue

Of the three significant arthropod-borne virus diseases presenting initially as FUOs, dengue was the most common. The fever, chills, and headache characteristic of most of the tropical diseases are also the most common manifestations of dengue. Dengue is usually acquired by a soldier residing in a large base encampment or urban area rather than in the jungle because the vector for dengue, the Aedes mosquito, is basically an urban dweller. The symptoms of dengue are not distinctive. Three-fourths of the patients have a "flu-like illness" with malaise, backache, anorexia, fever, and frequently severe frontal headache. They may present with lymphadenopathy, an important physical finding because patients with malaria do not have adenopathy, and patients with scrub typhus develop adenopathy generally several days after the onset of the illness. A fleeting macular rash is present in at least one-third of the patients and spontaneous petechiae occurring within this setting, especially on the lower extremities, provide good clinical evidence of an arbovirus disease. On occasion, the tourniquet test may be positive and unassociated with a reduction in platelet count. The course of dengue is usually short, fever is rarely over 104 F, symptoms subside within five to seven days, and few patients have a prolonged convalescence.

Occasionally a patient will show a slight fever elevation on the fifth day before a return to normal temperature by the seventh day. No specific therapy is indicated.

Chikungunya

Chikungunya disease was first recognized in Tanganyika in 1952 when an epidemic characterized by high fever and severe polyarthritis occurred among the natives. Specimens collected from affected patients and pools of Aedes mosquitos from this epidemic were subsequently analyzed and a new virus was recognized in 1956 to which the name *chikungunya* was given – the descriptive description of the disease which means "that which bends up the joints".

Since the recognition of that original epidemic, chikungunya disease has been identified throughout Southeast Asia, the Southern parts of Africa and India. It has had a wide spectrum of clinical features — severe polyarthritis (which, so far as I know, has been self-limiting), or a dengue-like illness with mild arthritis, or frank hemorrhagic fever. The same virus has been cultured from all these clinical varieties. The disease was not recognized in Americans in RVN before the study of Deller and Russell. /12/

One feature that distinguishes this disease from dengue is arthritis. Even though dengue has been referred to as "break-bone fever", it is

not associated with arthritis (severe myalgias and arthralgias may occur with dengue but not arthritis). The polyarthritis of chikungunya is an example of a known viral disease that can mimic rheumatoid arthritis or acute rheumatic fever and from which an organism can also be readily cultured. The arthritis of chikungunya may linger for several weeks following return of fever to normal and the disappearance of all other clinical manifestations. Except for the arthritis, the chikungunya in American troops has been a mild dengue-like illness. It has not produced the severe crippling arthritis of the type reported from the initial epidemic nor has it caused hemorrhagic fever. Like dengue, it requires no specific therapy.

Japanese B Encephalitis

A more recently recognized arbovirus disease, first appearing in epidemic form in the summer of 1969 in South Vietnam, is Japanese B encephalitis. /13/ This virus is carried primarily by the Culex mosquito vector. Although an epidemic encephalitis was recognized as a clinical entity in Japan as early as 1871, virus isolation and characterization did not occur until 1935. Japanese B encephalitis first became a military medical problem in American troops in Korea during the summer of 1947, and appeared also in 1948 and 1950. The classical presentation of Japanese B encephalitis in American troops has been a persistent headache followed by chills, fever, anorexia, general weakness, and nuchal stiffness. Within a few days following the onset of these symptoms, somnolence occurs. In most instances, the disease is self-limited with fever lasting seven to eight days and rapid recovery thereafter. However, in the Korean epidemic the summer of 1950, there were approximately 200 patients with Japanese B encephalitis of which 8.5 percent died.

In the more recent Vietnam experience, there have been several fatalities attributable to Japanese B encephalitis. An occasional case will have a more subacute onset, while, in contrast, a few cases may have a hyperacute onset with dramatic presentation of psychosis, seizures, and early death. In contradistinction to the other arbovirus diseases, leukocytosis is present in most of these cases (average peripheral white blood cell count of 13,000/cu mm). Spinal fluid in all cases shows a pleocytosis with a cell count of 10 to 2,000/cu mm and an average spinal fluid white cell count of 200/cu mm of which greater than 70 percent are polymorphonuclear leukocytes. The disease can be positively diagnosed by isolation of the virus from the blood or from tissues in autopsy cases. Specific serologic tests using neutralizing antibodies, complement fixation, and antihemagglutination techniques can confirm the diagnosis.

RICKETTSIAL DISEASES

Scrub typhus is caused by a mite-borne rickettsia (R tsutugamushi) and classically is manifested by a typical triad of rash, eschar, and a positive therapeutic response to tetracycline. With these features present, it is usually easy to diagnose. Unfortunately, not all cases present so clearly. Sometimes the eschars are hidden and may be overlooked on physical examination, or they may not be present at all especially in dark-skinned races Like malaria, scrub typhus is usually acquired by the combat soldier. The mites that carry the rickettsial organism breed in heavily forested areas of Vietnam. Hence, the history of exposure to the jungle environment is important. The fever, chills, headache, malaise, adenopathy, and backache common to the other tropical diseases are also characteristic of scrub typhus. Severe retro-orbital headache is generally the most prominent complaint. Patients frequently also have marked conjunctival suffusion which adds to confusion in differentiating this disease from leptospirosis. Cough and dyspnea are also common symptoms. The most important feature on physical examination is the eschar which typically resembles a cigarette burn. It is usually painless, has a black, necrotic center with a narrow rim of erythema. A macular rash, which is not as fleeting as the rashes of the arbovirus diseases and does not become confluent, is also a diagnostic sign Lymphadenopathy and splenomegaly are occasionally found. Early recognition of this disease is important because, when treated promptly, it responds dramatically to tetracycline therapy (1.0 gm every hour for 4 doses followed by 1.0 gm every 6 hours for 5 to 7 days). Within 48 hours, and often within 12 hours, there is a dramatic lysis in fever. It is important to treat scrub typhus early because if the disease goes untreated for more than ten days to two weeks, there is an alarming morbidity and occasional mortality. Those patients in whom the disease is not recognized and treated early will require prolonged convalescence. Definitive diagnosis requires specific serological testing (the results of which are not immediately available). Thus, a trial of therapy with tetracycline is warranted when there is a strong clinical suspicion of scrub typhus.

In Southeast Asia, human cases of *murine typhus* have been reported from Maylasia, the Philippines, and Thailand. /16/ Murine typhus (R. mooseri) is probably the rickettsial disease most apt to be confused clinically with scrub typhus. Epidemiologically, however, these two conditions are quite different in that murine typhus is generally "urban-acquired" from the infected rat flea while scrub typhus is generally "jungle-acquired". The diagnostic hallmark of scrub typhus, the eschar, is absent in murine typhus. Since this is not an invariable feature, its absence alone cannot be relied upon to make a differential diagnosis

and clinically there is little else to distinguish these two illnesses. Thus, the final diagnosis must rest with the laboratory. Agglutinins against the OXK strain of Proteus vulgaris occur in the serum of patients with scrub typhus and against the OX19 strain in murine typhus. The most definitive finding, however, is a four-fold rise in titer during convalescence against specific complement fixing antibodies, or the isolation of the specific rickettsial agents. As previously noted, the results of these specific laboratory tests are not immediately available to help diagnose the condition in the patient. Although in most cases this disease is uncomplicated and self-limited, tetracycline therapy will speed recovery when initiated early.

It is difficult to state with any certainty whether or not murine typhus was present to any degree in RVN during the initial FUO studies but could have been present and missed because the Weil-Felix reaction was not part of the screening procedures and specific complement fixation tests for murine typhus were not performed. The disease did appear later and was uncovered in the FUO study of Deaton /9/ (Table 2). In retrospect, it is likely that a number of cases which remained as self-limited TUFs in the earlier studies may have been caused by the Rickettsia mooseri.

Leptospirosis

Leptospirosis is most commonly acquired in Vietnam by combat troops who come in contact with the leptospires breeding in mud banks and rice paddys. Leptospirosis closely mimics dengue and scrub typhus and has few distinguishing characteristics of its own. Profound myalgias, however, constitute the most distinctive symptom. Patients generally have a spiking temperature and often a saddleback fever curve similar to that which occurs in scrub typhus. Conjunctival sufusion is an important sign and is frequently associated with blurred vision. Gastrointestinal complaints and hepatic tenderness are common but make the differentiation from malaria difficult. A laboratory finding of leukocytosis is occasionally helpful since most of the other tropical diseases (except Japanese B encephalitis) are characterized by normal leukocyte counts or by leukopenia. However, a normal count is present in approximately one-half of the cases. Leptospirosis actually encompasses an entire spectrum of disease from a benign, self-limited form, such as our troops experienced in Vietnam, to a more severe hemorrhagic disease with deep jaundice and renal failure. Since our troops, fortunately, acquired the benign form, there have been no serious complications. The benign form of leptospirosis is self-limited and requires no specific therapy.

Some of the major differential features of the five most important illnesses which present as tropical FUOs are presented in Table 4.

TABLE 4

DIFFERENTIAL FEATURES OF PATIENTS HAVING DENGUE, CHIKUNGUNYA, SCRUB TYPHUS, LEPTOSPIROSIS, AND MALARIA

	DISEASES				
	Dengue	Chikungunya	Scrub Typhus	Leptospirosis	Malaria
Exposure History					
Camp, urban	†††	†††	–	–	–
Jungle	–	–	†††	†††	†††
Signs/Symptoms					
Fever, Fahrenheit					
<104	†††	†††	†	†††	–
>104	–	–	††	–	†††
Arthralgias	–	†††	–	–	–
Tender adenopathy	††(Early)	†††	†††(Later)	†	–
Tender liver or spleen	–	–	††	††	†††
Rash	†	††	††	–	–
Petechiae or positive tourniquet test	†	–	–	–	–
Leukocyte count, per cu mm					
<5,000	††	††	–	–	–
>5,000, <10,000	†	†	†††	†††	†††

Legend: – = less than 25 percent; † = 25 to 49 percent; †† = 50 to 74 percent; ††† = 75 to 100 percent of the cases

LESSONS OF HISTORY

There are several lessons to be learned from our experience in Vietnam with fevers of undetermined origin. (1) We should maintain a nucleus of tropical disease experts from one generation to the next and maintain an awareness and an expertise of the major tropical diseases that might be encountered on future ventures into tropical countries. (2) We should maintain a surveillance of tropical disease problems world-wide so that one can accurately predict what diseases might be encountered in various areas of the world. (3) We should support on-going medical research studies in under-developed countries as an extension of knowing what major tropical disease exists throughout the world. These can lead to eradication of these diseases to those countries. (4) We should have properly equipped laboratories for the study of tropical disease problems and these should accompany initial military units into all tropical environments so that potential unfamiliar medical problems can be immediately spotted and recognized and perhaps prevented. (5) Surveillance and "keeping up" are not enough — in themselves — we should put this knowledge to use by seeking methods for prevention and control of all major tropical disease problems, especially in the area of immunology as well as in the broader scope of public health.

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POTENTIAL MEDICAL PROBLEMS IN RETURNING AMERICAN PRISONERS OF WAR

MAJ Carl C. Peck, MC

Letterman General Hospital, as well as selected other military hospitals, will soon be faced with the responsibility of providing medical care for repatriated Americans returning from prison camps in North Vietnam and neighboring countries. In addition to the psychological effects of prolonged internment, these men may suffer from certain medical conditions peculiar to their confinement experience in Southeast Asia.[1,2]

As our troop involvement in the Indochina conflict diminished throughout the past year, so did the Medical Corps' encounter with patients suffering from diseases indigenous to Southeast Asia. Many Medical Corps officers expert in the diagnosis and treatment of these diseases have left the Armed Forces by virtue of retirement or completion of tours of duty. Moreover, physicians may not be familiar with the dietary deficiency syndromes with which some repatriated prisoners of war may present.

Thus, a brief review of each of these potential medical problems is presented in the following pages. Capsule summaries, containing salient features of these conditions, are designed for quick reference. Not included are diseases commonly seen in the United States to which these men may also be subject, i.e. hepatitis, hypertension, and arteriosclerotic heart disease. The acute febrile diseases are presented first since returnees will be at risk for most of these only during the first three weeks following release. The exception is malaria which may appear *de novo* anytime up to two years following exit from an endemic area.

Contents

Contents, concluded

Potential Medical Problems - Peck

MALARIA (*Plasmodium*)[3]

Incubation time 8 to 14 days; however, occasionally malaria presents anew anytime within two years following exit from endemic area.

Symptoms Episodic high fever (104°+ F., 40°+ C.) and vigorous shaking chills interspaced with afebrile periods of apparent well-being
More chronic cases may have only low grade fever and anemia

Signs Remarkable absence of positive findings
± hepatic tenderness
± splenomegaly

Laboratory Diagnosis Identification of parasites in red blood cells in peripheral thin smear (Wright's or Giemza stains). Thick smear (Giemza) is useful when parasite density is low.

NOTE: Species identification is essential. *Falciparium* malaria may be *FATAL*.

Indirect fluorescent antibody test for malaria.

Treatment Species identification determines appropriate treatment.

p. vivax only...

Chloroquine phosphate	1.0gm STAT 0.5gm in 8 hr 0.5gm qd x 2d
plus	
Primaquine phosphate	26.3mg qd x 14d

p. falciparium only...

Quinine sulfate	650mg q 8 hr x 10d
Pyramethemine	25mg q 12 hr x 3d
Gantrisin®	500mg q 6 hr x 7d

Mixed *vivax* and *falciparum*...
Treatment for *falciparum* + Primaquine 26.3 mg qd x 14d

NOTE: All returnees should receive the usual end-of-tour terminal prophylaxis, consisting of:
Chloroquine phosphate 1.0 gm, single dose
Primaquine phosphate 26.3mg qd x 14d

Potential Medical Problems - Peck

DENGUE (*Arbovirus*)[4]

Incubation time	3 to 15 days
Symptoms	Fever (not greater than 103° F., 38.4° C.), chills Severe retroorbital headache Severe myalgias
Signs	Muscle and skin tenderness Lymphadenopathy Relative bradycardia ± fleeting rash, petechiae ± positive tourniquet test
Diagnosis	Clinical Hemagglutination test for Dengue
Treatment	Supportive (Bed rest, ASA) Fever usually lasts 5 to 7 days

Potential Medical Problems - Peck

SCRUB TYPHUS (*Rickettsiae*)[4]

Incubation time	7 to 18 days
Symptoms	Fever, chills Retroorbital headache Backache ± cough, dyspnea
Signs	± eschar (like a cigarette burn) ± macular rash ± lymphadenopathy, splenomegaly
Diagnosis	Clinical Indirect fluorescent antibody test for Scrub Typhus
Treatment	Tetracycline 1.0gm q 4 hr x 4 doses *then* 1.0gm q 6 hr x 5-7 days

NOTE: An untreated case may lead to chronic debility with slow spontaneous recovery.

Potential Medical Problems - Peck

LEPTOSPIROSIS (*Leptospira*)[4]

Incubation time	6 to 12 days
Symptoms	Fever, chills Myalgias Prostration + nausea, vomiting
Signs	Conjunctival suffusion Relative bradycardia Tender muscles ± meningeal signs ± jaundice
Diagnosis	Clinical Culture of blood and cerebrospinal fluid on Fletcher's media Leptospiral antibody test
Treatment	No treatment necessary for benign form. Severe form may respond to. . . Penicillin 3 million units per day and Streptomycin 2 grams per day *OR* Tetracycline 2 grams per day

Potential Medical Problems · Peck

CHICKUNGUNYA FEVER *(Arbovirus)*[4]

Symptoms	Fever, chills Arthralgias ± headache, myalgias
Signs	Polyarthritis *plus* same as Dengue (Muscle and skin tenderness Lymphadenopathy Relative bradycardia ± fleeting rash, petechiae ± positive tourniquet test)
Diagnosis	Clinical Hemagglutination test for Chickungunya
Treatment	Supportive. Fever usually last 5 to 7 days; arthritis may persist longer.

Potential Medical Problems - Peck

JAPANESE B ENCEPHALITIS (*Arbovirus*)[4]

Symptoms	Headache, stiff neck Chills, fever Somnolence
Signs	Nuchal rigidity Reduced conciousness
Diagnosis	Clinical Abnormal cerebrospinal fluid Hemagglutination test for Japanese B virus
Treatment	Supportive Permanent neurologic and psychologic residua may occur

Potential Medical Problems - Peck

PLAGUE (*Pasteurella pestis*)[5]

Plague is considered because of its endemicity and the likelihood that some of our POWs will have been interned in prison cells infested with rats. Bubonic, septic, and pneumonia are clinic presentations.

Incubation time	2 to 10 days
Symptoms	History of rat bite or exposure to rat-infested area Fever Headache Anxiety Swelling of groin or armpit Cough with bloody sputum (Pneumonic plague–rare) Toxemia
Signs	Inguinal, axillary, or cervical adenitis (Bubonic) proximal to rat bite
Diagnosis	Clinical Culture of *P. pestis* from bubo-aspirate, blood, or sputum Microscopic examination of Gram-stain reveals a bipolar pleomorphic gram-negative bacillus
Treatment	Streptomycin in combination with tetracycline.

MALNUTRITION[6-9]

The diet of the working classes and of the military in Southeast Asia frequently is borderline or deficient in essential nutrients. An extensive survey of the nutrient intake, nutritional problems, and nutritional status of both the civilian and military population in RVN was conducted in 1959 which helped to pinpoint potential or actual problems in nutrition in this area of the world. The normal diet is low and sometimes deficient in thiamine, riboflavin, vitamin A, vitamin C, calcium and iron. Many of the endemic diseases impose an increased requirement for specific nutrients, while a deficient or borderline intake of some nutrients increases the susceptibility of the individual to infectious disease.

Few of the physical signs that are associated with malnutrition are in themselves pathognomic of a specific deficiency, while most are associated with multiple deficiencies. Many of the signs may be overlooked unless specific effort is made during the physical examination. The medical record, prepared by the Center for Prisoners of War, is designed to detect systematically symptoms and signs of these potential nutritional deficiencies. Moreover, a biochemical survey of certain serum vitamin levels is recommended for the immediate post-release period. Although not available for acute care diagnosis, results of these tests may ultimately help explain transient or permanent defects resulting from dietary deficiencies.

Potential Medical Problems - Peck

PROTEIN-CALORIC DEPRIVATION[7]

Symptoms	Weight loss Weakness, lassitude
Signs	Wasting, muscle atrophy ± edema–anasarca ± thinning/loss of body hair ± flaky dermatitis ± hepatomegaly
Diagnosis	Clinical
Treatment	Balanced, calorically adequate diet. Special diets probably not necessary.[2p1065]

Potential Medical Problems - Peck

VITAMIN A DEFICIENCY (carotene)[8]

Symptoms	Night blindness Dry, burning eyes (xerophthalmia) Blindness (late)
Signs	Dryness of the conjunctiva (xerosis) and/or the cornea Decreased tearing Corneal softening (Keratomalacia), blindness and ulceration Hyperkeratosis of lower arms, upper forearms, buttocks, anterolateral and posterior thighs Patchy decoloration of the buccal mucosa (up to and including leukoplakia)
Diagnosis	Clinical Loss of dark adaptation Serum Vitamin A levels
Treatment	Vitamin A 22.5 mg/day orally or intramuscularly Eye care as indicated (synthetic tears, antibiotics, etc.)

Potential Medical Problems · Peck

VITAMIN B_1 DEFICIENCY SYNDROMES (thiamin)[6,9]

Beriberi

Symptoms	Easy fatigability, palpitations, ankle swelling
	Swelling of legs, scrotum, face, trunk ("wet" beriberi)
	Dyspnea on exertion, orthopnea
	Numbness, tingling in feet ("dry" beriberi, but may occur in both dry and wet beriberi)
	Incoordination
Signs	Signs of congestive heart failure
	Anasarca ("wet" beriberi)
	Ataxia ("dry" beriberi)
	Foot and wrist drop
	Anesthesias
	Muscle tenderness and weakness of calf muscles
	Alteration or absence of deep tendon reflexes of lower extremities
	Loss of vibratory sense – distal extremities

Wernicke-Korsakoff (W-K) Syndrome

Symptoms	Double vision
	Incoordination
	Poor memory
Signs	Nystagmus, ophthalmoplegias
	Ataxia
	Deficient memory and confabulation
Diagnosis	(applicable to beriberi and W-K syndrome)
	Clinical
	Urinary levels of thiamine
	Red blood cell transketolase determination with and without stimulation with thiamine pyrophosphate
Treatment	Thiamine 10-20 mg/day intramuscularly
	Digitalis and diuretics usually not necessary

Potential Medical Problems - Peck

RIBOFLAVIN DEFICIENCY

Symptoms	Sore lips, mouth, skin and genitalia, photophobia, excess lacrimation, itching and burning of eyes
Signs	Angular stomatitis–bilateral* Cheilosis–edema and chapping of lips, flaking or crusting, painful red cracks of lips Glossitis Scaly, scrotal dermatitis Corneal vascularization Keratin plugged sebaceous glands of nasolabial folds, canthi of eyes and ears
Diagnosis	Clinical Urinary riboflavin levels Red blood cell glutathione reductase with and without stimulation with flavine adenine dinucleotide
Treatment	Riboflavin 3-5 mg/day

* Fissures radiating from angles of mouth onto skin and often into oral mucosa.

Potential Medical Problems - Peck

NIACIN DEFICIENCY OR PELLAGRA (nicotinic acid)[8]
4"D's" = Dermatitis, Diarrhea, Dementia, Death

Symptoms	Skin complaints Diarrhea, abdominal pain, sore tongue Memory loss, irritability, anxiety
Signs	Dry scaly dermatitis of those parts of the body exposed to sunlight, heat or mild trauma. Symmetrical distribution Smooth red tongue Dementia, mild sensory abnormalities
Diagnosis	Clinical
Treatment	10-15 mg nicotine acid/day

Potential Medical Problems - Peck

PANTOTHENIC ACID DEFICIENCY [8]

Symptoms	Burning and paresthesias of hands and feet Gastrointestinal complaints
Diagnosis	Clinical
Treatment	Balanced U.S. diet automatically contains 10-15 mg per day

Potential Medical Problems - Peck

VITAMIN B_6 Deficiency (pyridoxine)[8]

Clinical Conditions Associated with B_6 Deficiency	Convulsive seizures Painful plyneuritis (as in INH therapy)
Signs	Nasolabial seborrhea and seborrheic dermatitis Deep tendon reflex changes
Diagnosis	Clinical Urinary excretion of pyridoxine Xanthurenic acid, excretion after tryptophane loading
Treatment	Vitamin B_6 2.5 mg per day

Potential Medical Problems - Peck

VITAMIN B_{12} DEFICIENCY (cyanocobalamin)[8]

Symptoms	Weakness Sore tongue and mouth, minor gastrointestinal disturbances Numbness, paresthesias, incoordination
Signs	Pallor Inflamed, smooth tongue Cardiovascular manifestations of anemia Loss of vibratory sense, pain, anesthesia, ataxia, spasticity
Diagnosis	Peripheral smear: Macrocytic red blood cells, hypersegmented polymorphonuclear leukocytes, leukopenia Abnormal hemoglobin/hematocrit, red blood cell indices Megaloblastic bone marrow Serum B_{12} level
Treatment	B_{12} 2-4 micrograms per day

Potential Medical Problems - Peck

FOLATE DEFICIENCY (folic acid) [8]

Symptoms	**Weakness** Gastrointestinal (GI) symptoms
Signs	Same as in B_{12} deficiency except no neurologic abnormalities and GI symptoms may be more severe
Diagnosis	Peripheral smear: macrocytic red blood cells, hypersegmental polymorphonuclear leukocytes, leukopenia Reduced hemoglobin, hematocrit, and altered red blood cell indices Megaloblastic bone marrow Serum folate level
Treatment	Folic acid 0.5 mg per day

Potential Medical Problems - Peck

VITAMIN C DEFICIENCY (ascorbic acid)[8]

Symptoms	Weakness, fatigue, listlessness Joint and foot pains Sore gums Generalized bleeding tendency Skin complaints
Signs	Petechiae, particularly of lower extremities Coiled imbedded hairs Hyperkeratosis Muscle tenderness and weakness Swelling and tenderness of joints Edema (occasionally unilateral) Marked cardiovascular sensitivity to cold Spongy, swollen, red, interdental papillae
Diagnosis	Clinical Plasma ascorbic acid levels NOTE: Sudden cardiovascular collapse may occur
Treatment	Ascorbic acid 1000 mg STAT, 250 mg every 6 hours x 7 days, then 50 mg per day until complete recovery Parenteral administration may be necessary for first 24 hours, then orally in divided doses

Potential Medical Problems · Peck

VITAMIN D DEFICIENCY (calciferol)[8]

Symptoms	Bone pains in pelvis, lower back and legs
Signs	Bone tenderness Pelvic and spinal deformities Pathologic fractures Involuntary twitches of facial muscles and carpopedal spasms
Diagnosis	Radiographic evidence of demineralization Deformities, idiopathologic fractures Increased serum alkaline phosphatase Decreased serum calcium
Treatment	Vitamin D 125 mg, milk (calcium lactate) Sunlight to skin

Potential Medical Problems - Peck

VITAMIN K DEFICIENCY[8]

(Deficiency rarely occurs due to dietary insufficiency, but may accompany malabsorption states such as sprue)

Symptoms	Bleeding diathesis
Diagnosis	Prolonged prothrombin time
Treatment	10 mg Vitamin K per week

Potential Medical Problems - Peck

IODINE DEFICIENCY (endemic goiter)[8,9]

Symptoms/Signs	Thyroid enlargement
Diagnosis	Clinical Full thyroid evaluation to rule out carcinoma
Treatment	Delayed pending completion of diagnostic evaluation.

NOTE. Though endemic goiter is not uncommon in Vietnam, it is certainly not life threatening and in only a few cases of marked severity and prolonged duration has there been a significant decrease in thyroid function. On the other hand, treatment with thyroid extract may complicate the cardiovascular problem and exacerbate some of the other deficiencies that may be present.

-Canham[6]

Potential Medical Problems - Peck

IRON DEFICIENCY[8]

Symptoms	Weakness, fatigue, lassitude Dyspnea on exertion Palpitations Soreness of the tongue
Signs	Angular stomatitis, bilateral (see Riboflavin deficiency) Atrophy of papillae of the tongue Changes in fingernails–brittle, spoon shaped Pallor
Diagnosis	Clinical Peripheral smear, hypochromic, microcytic red blood cells Low hemoglobin, hematocrit Serum iron and percent transferrin saturation
Treatment	Depends on severity. Mild to moderate anemia (down to 9 gm% hemoglobin) generally is corrected by adequate diet, elimination of intestinal parasites or other cause of blood loss, and oral iron therapy

Potential Medical Problems - Peck

CALCIUM DEFICIENCY[6]

The dietary intake of calcium in Southeast Asia is generally low and may pose a problem particularly in prisoners in captivity for long duration. A normal or high intake of NaCl may precipitate symptoms of deficiency.

Potential Medical Problems- Peck

In addition to dermatologic manifestations of some of the infectious diseases (rashes, eschar) and of various vitaminoses some primary dermatologic conditions may be encountered in returning POWs, e.g. pyoderma, dermatophytosis, tropical immersion foot, and leprosy.

PYODERMA [16]

Symptoms	Painful, superficial sores, especially on extremities ± history of trauma
Signs	Purulent ulcerations Discrete, "punched out" lesions which are oval 0.5 - 3.0 cm in diameter with surrounding erythema and induration ± regional lymphadenopathy
Diagnosis	Clinical Bacteria culture and sensitivity may reveal high prevalence of Group A-B hemolytic streptococci and *Staphylococcus aureus.* NOTE: Melioidosis, especially in infected wounds, is a possibility that should not be overlooked.
Treatment	Local care: frequent debridement, ± topical antibiotics ± systemic antibiotics (penicillin, tetracycline)

Potential Medical Problems - Peck

DERMATOPHYTOSIS (*fungal dermatitis*)[10]

Symptoms	Painful, red rash in groin, buttocks, dorsa of feet and legs
Signs	Erythematous dermatitis ± purulent superinfection
Diagnosis	Demonstration of fungi in potassium hydroxide (KOH) preparations of scrapings Fungal culture of scrapings or hairs from affected areas
Treatment	May respond to topical application of tolnaftate (Tinactin ®) More severe infections may require systemic administration of griseofulvin

Potential Medical Problems - Peck

TROPICAL IMMERSION FOOT [10]

Symptoms	History of prolonged immersion of feet in water Painful, swollen, red, feet and ankles ± fever ± tenderness and swelling in groin
Signs	White, macerated plantar surfaces ± pitting edema of feet and ankles ± maculopapular rash
Diagnosis	Clinical NOTE: Tropical immersion foot applies only to physical effects of water immersion and should not include infections
Treatment	Bed rest Elevation of feet

Potential Medical Problems - Peck

LEPROSY (*Mycobacterium leprae*)

Although leprosy is one of the least contagious of all the infectious diseases, it is reported as a "common disease" in North Vietnam and therefore is included here.

Symptoms	Patchy numbness Spots, hypopigmented or red Thickening of skin Loss of eyebrows
Signs	Progressive loss of heat/cold discrimination, pain, then loss of tactile sense in affected areas Induration in affected areas (especially earlobes, eyebrows) Thickening and tenderness of peripheral nerve trunks (especially ulnar, external peroneal, and great auricular nerves) Collapse of nasal cartilage
Diagnosis	Demonstration of the acid-fast, gram-positive, bacillus of *M. leprae* in smears from lesions or biopsies
Treatment	Dapsone *or* Rifampin

Potential Medical Problems - Peck

TUBERCULOSIS[11,12]

While tuberculosis (TB) has not been a problem of great magnitude in soldiers serving a 13-month "hardship" assignment in Republic of Vietnam (RVN), it is possible that it will emerge as a significant problem among returning POWs. This fear is based on the high prevalence of TB as a cause of morbidity and mortality in studies of the indigenous Vietnamese population.[11]Prolonged detention and contact with Vietnamese natives suggests that this fear may be realized. Moreover, it is estimated that as much as 25 percent of the active TB in RVN is primary drug-resistant.[12]Thus, special emphasis in detecting the presence of active tuberculosis will be offered our returning POWs.

TB patients will be treated at the TB treatment centers of the respective services (Army - Fitzsimons General Hospital, Valley Forge General Hospital; Air Force - Scott Air Force Base; Navy - St. Albans).

Symptoms	Cough ±production of bloody sputum ±weight loss
Signs	Abnormal chest examination Hemoptysis Cachexia
Diagnosis	Abnormal chest x-ray Positive skin test Acid-fast bacilli in sputum Positive TB cultures of sputum
Treatment	(Minor variations may occur depending upon the fashion at the treatment center) First line drugs – INH, ethambutol, streptomycin, PAS Second line drugs – Rifampin

Potential Medical Problems - Peck

MELIOIDOSIS[13]

Pseudomonas pseudomallei is a gram negative bacillus which causes a variety of pathologic conditions in man. Because of its often obscure presentation, and its discovery in a number of American soldiers serving in RVN, diligent awareness of its potentialities on the part of examining medical officers will preclude its being missed as a cause of disease in returning POWs.

CLINICAL VARIETIES

- Septicemia
  A fulminant septic disease accompanied by signs of miliary visceral and septic emboli of highly fatal consequences if it is not recognized and treated promptly. Meningoencephalitis, myocarditis, and a terminal pneumonia may result.
- Acute melioid-pneumonia. This is a rapidly progressive fulminant pneumonia.
- Chronic melioidosis
  More common than the acute forms. Chronic pulmonary melioidosis closely simulates tuberculosis, both clinically and radiographically. Chronic infections of bones or joints or unhealing cutaneous wounds may be caused by *P. pseudomallei*. These lesions may lie dormant for a long period of time then flare into acute forms.

Diagnosis

High index of suspicion is essential since clinical laboratories may not recognize it when present. The possibility of its presence must be indicated to laboratory personnel so it will be pursued. *P. pseudomallei* may be cultured on blood agar plates or in thioglycolate broth. Microscopic examination reveals a small, pleomorphic, gram-negative rod that has bipolar staining properties.

Serologic testing for melioidosis with rising titers may be helpful in diagnosis.

Treatment

Sensitivities should be ascertained by culture.

Tetracycline, chloramphenicol, kanamycin, novobiocin have all shown potent activity against most strains. Chronic cases have been successfully treated with tetracycline 3.0 gm per day.

Potential Medical Problems - Peck

AMEBIASIS[14]

INTESTINAL AMEBIASIS (*E. histolytica*)

Symptoms	May be asymptomatic Loose stools ranging to frank dysentery Stool frequently bloody Abdominal cramping and pain
Signs	± hyperperistalsis, abdominal tenderness
Diagnosis	Demonstration of cysts or motile trophozoites of *E. histolytica* in *fresh* stool (most reliably obtained by swap of rectal ulcers per proctosigmoidoscopy). Gross blood or occult blood-positive stool Indirect fluorescent antibody test for Amebiasis
Treatment	Asymptomatic intestinal ambebiasis: Metronidazole (Flagyl ®) 400-800mg t.i.d. x 5d *OR* Diloxanide 0.5gm t.i.d. x 10d Amebic dysentery: Metronidazole 2.0-2.4gm as single dose x 3d *OR* Metronidazole 800mg t.i.d. x 5d

Potential Medical Problems · Peck

AMEBIASIS[14]

AMEBIC LIVER ABSCESS

Symptoms	Weight loss Right upper quadrant pain ± history of bloody diarrhea ± low grade fever ± right shoulder pain (referred)
Signs	Hepatomegaly, hepatic tenderness Evidence of elevated right hemidiaphragm
Diagnosis	Liver abscess demonstrated by liver scan Right hemi-diaphragmatic elevation on chest x-ray Indirect fluorescent antibody test for Amebiasis
Treatment	Metronidazole 400mg t.i.d. x 5d *OR* Metronidazole 2.0-2.4gm as single dose x 2-3d Closed aspiration may be required in some cases Response to therapy may be judged by resolution of abnormal liver scan

Potential Medical Problems - Peck

BACTERIAL DIARRHEA

TYPHOID, PARATYPHOID FEVERS (*Salmonella species*)[15-17]

Symptoms	Gastrointestinal complaints, later overshadowed by systemic complaints of fever, headache, cough, "rose-colored spots"
Signs	Abdominal tenderness and distension, Maculo-papular rash Rales and rhonchi Blood in stool Relative bradycardia
Diagnosis	Clinical Bacterial culture of stool Febrile agglutinins
Treatment	Chloramphenicol remains the drug of choice Ampicillin is clinically inferior even though in vitro sensitivity testing shows activity against *S. Typhosa.*[15]
	NOTE: Treatment of asymptomatic salmonella excreters and simple salmonella gastroenteritis is not advised.[16,17]

Potential Medical Problems - Peck

BACTERIAL DIARRHEA

BACILLARY DYSENTERY (*Shigella species*)[17]

Symptoms	Fever, tenesmus Blood- and mucus-containing dysentery
Signs	Lower abdominal tenderness Blood in stool ± signs of dehydration
Diagnosis	Culture of stool
Treatment	Supportive. Antibiotic treatment is not indicated unless there is evidence of systemic or parenteral invasion.[17]

Potential Medical Problems - Peck

BACTERIAL DIARRHEA

CHOLERA (*Vibrio comma*)[18]

Symptoms	Painless, fulminant, explosive (rice-water) dysentery, frequently accompanied by vomiting
Signs	Signs of severe dehydration Cyanosis Hypopyrexia
Diagnosis	Clinical Bacterial culture of stools (GTT agar) Microscopic identification of "comma-like" gram-negative rod Fluorescent antibody titers may assist in making rapid diagnosis
Treatment	Survival depends upon maintaining proper fluid and electrolyte balance Tetracycline given early in the disease may diminish the duration of the diarrhea

Potential Medical Problems - Peck

HOOKWORM DISEASE (*Necator americanus, Ancylostoma duodenale*)[19]

A high incidence of hookworm infestation is expected. Hookworm enters the body through the skin (feet) upon contact with soil containing human feces. Following circulation to the lungs, the parasite migrates up the respiratory passages to the esophagus and back into enter the digestive tract.

Symptoms	May be asymptomatic Weakness, palpitations Epigastric discomfort
Signs	± pallor
Diagnosis	Demonstration of hookworm ova in stool Stool positive for blood Mild eosinophilia is common Anemia
Treatment†	Tetrachloroethylene 0.12ml/kg (max 5ml) as single oral dose *OR* Bephenium 5gm b.i.d. x 3 d

Potential Medical Problems - Peck

STRONGYLOIDIASIS (*Strongyloides stercoralis*)[19]

Similar to hookworm, the larvae of this parasite enters the host through the skin (feet) and follows the same migratory pattern through respiratory passages to its final gastric and intestinal implantation.

Symptoms	May be asymptomatic ± epigastric pain
Signs	±epigastric tenderness
Diagnosis	Demonstration of mobile rhabditiform larvae in the stool May also be recovered by duodenal aspiration A mild eosinophilia is a frequent accompaniment
Treatment	Thiabendazole (Mintezol ®), 25 mg/kg b.i.d. for 2 days

ASCARIASIS (*Ascaris lumbricoides*)[19]

Uncooked vegetables soiled by human excreta are a source of these ingested parasite ova. From the gastrointestinal tract, larvae circulate to the lungs, then migrate up the respiratory tree to reenter the gastrointestinal tract again.

Symptoms	May be entirely asymptomatic Fever Cough Hemoptysis (accompanying larval migration to lungs) Abdominal colic Passage of "worms" rectally
Signs	Signs of intestinal obstruction ± signs of atypical pneumonia ± abdominal tenderness, distension (rarely)
Diagnosis	Demonstration of ova or adult worm in stool
Treatment†	Piperazine citrate, 75 mg/kg (maximum 3.5 gm) daily for two days

Potential Medical Problems - Peck

WHIPWORM OR TRICHURIASIS (*Trichuris trichiura*)[19]

Trichuris ova are ingested via food contaminated by infected human excreta. Eggs hatch in the duodenum then migrate to their adult habitat, the cecum and proximal colon.

Symptoms	Usually asymptomatic Severe infestations can result in diarrhea, abdominal pain, anemia, and even rectal prolapse
Signs	Dependent upon severity of infestation
Diagnosis	Demonstration of characteristic double-shelled, bile-stained eggs with mucoid plugs. ± eosinophilia
Treatment	Hexylresorcinol (0.3% solution), 500 ml by rectal retention for one hour

Potential Medical Problems - Peck

PORK, BEEF TAPEWORM INFECTION (*Taenia solium, T. saginata*) [19]

Tapeworm infection occurs upon ingestion of raw pork or beef from infected cattle which have grazed on grasses contaminated by ova containing human excreta. Although tapeworm infection is endemic to some Southeast Asian countries, it is anticipated that our POWs are seldom offered meat in their diet.

Clinical picture	May be asymptomatic Gastrointestinal symptoms Signs of malnutrition Dissemination of embryos (*cysticercus*) via circulation to muscle, subcutaneous tissues, or brain can cause specific symptoms and signs in these areas: : myalgia, vertigo, headache
Diagnosis	Recognition of Taenia ova in stool establishes the diagnosis but specific identification of species is based on differentiation of mature proglottides
Treatment	Quinacrine hydrochloride, 200 mg x 4 doses, 10 minutes apart; 600 mg sodium bicarbonate with each dose

Potential Medical Problems - Pack

CHINESE LIVER FLUKE DISEASE OR CLONORCHIASIS (*Clonorchis sinensis*)[19]

If our POWs have been offered raw or undercooked fresh water fish which are infected with clonorchis cysts, clonorchiasis may result. The parasites migrate from the duodenum into biliary radicals whereupon the liver reacts with cell proliferation and desquamation

Symptoms	Fever Epigastric pain Diarrhea Episodes of jaundice Later stages—anemia, weight loss
Signs	Hepatomegaly ± icteris Later stages—ascites —cachexia
Diagnosis	Ova in stool or bile/duodenal aspirates
Treatment	Chloroquine phosphate, 250 mg t.i.d. for 6 weeks

Potential Medical Problems - Peck

TROPICAL SPRUE[20]

This is a malabsorption syndrome resulting from protracted stays in tropical areas associated with nutritional deficiencies and bacterial contamination.

Clinical Picture	May be asymptomatic during ititial period of return to the United States
	Progressive symptoms: Fatigue, bulky stools–weight loss, steatorrhea *with the eventual development of* malabsorption with megaloblastic anemia
Diagnosis	Definitive diagnosis rests upon demonstration of villous atrophy in small bowel biopsy and positive response to broadspectrum antibiotics
	Supportive evidence include decreased d-Xylose absorption, decreased albumin, carotene, increased stool fat content
Treatment	Broad spectrum antibiotics (tetracycline), folic acid, and B_{12} (initially by injection)

Potential Medical Problems - Peck

TRACHOMA (*TRIC agent*)

Trachoma, a chronic infectious disease of the conjunctive and cornea, is reportedly widespread in North Vietnam. This "granular" conjunctivitis can progress to involve the cornea with eventual blindness.

Diagnosis	Clinical: Triad of criteria = (1) follicular hypertrophy, most prominent on upper tarsal conjunctiva; (2) pannus formation, and (3) conjunctival scars
	Intracytoplasmic inclusions in conjunctival or genital cells may be demonstrated; particularly sensitive is the immunofluorescent stain
Treatment	Topical 15% sodium sulfacetamide and systemic treatment with a sulfa or tetracycline antibiotic

Potential Medical Problems - Peck

FILARIASIS (*Wuchereria bancrofti; Brugia malavi*)

Filariasis is an inflammatory disease of the lymphatic system of man resulting from dermal innoculation of the parasites via a mosquito bite. The larvae mature in the lymphatic system releasing micro-filariae in peripheral blood.

Clinical picture	Early stage -	lymphangitis lymphadenitis orchitis epididymitis fever
	Late stage -	massive extremity or scrotal edema (elephantiasis)
Diagnosis	Early - demonstration of microfilarial in blood (Wright's or Giemza stain) Late - clinical	
Treatment	Diethylcarbamazine, 2 mg/kg t.i.d. for about 14 days	

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MALARIA
Return of an Old Problem to the American Physician

MAJ Carl C. Peck, MC USAR
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Malaria is the number one infectious disease problem in the world; presently there are approximately 100 million cases annually. One million deaths result from the disease per year. /1/ While malaria remains a major health problem in many tropical countries, it has been some years since the disease has caused concern to physicians practicing within the United States. Review of Table 1 brings the problem into historical perspective and justifies terming malaria "an old problem to the American physician".

TABLE 1 /2,3/
CASES OF MALARIA IN UNITED STATES

YEAR	CASES	YEAR	CASES
1943	400,000	1960	72
1945	62,763	1963	99
1950	2,184	1964	93
1955	522		

Malaria has obtained particular significance in wartime. During World War II in the South Pacific, the attack rate of malaria in the United States Armed Forces was five times the number of combat casualties. The conflict in Southeast Asia has been no exception. During 1965 the number of soldiers evacuated from Vietnam because of malaria was equal to the number evacuated for battle wounds. /4/ Table 2 dramatically demonstrates the "return" of malaria to America.

TABLE 2

CASES OF MALARIA DIAGNOSED
WITHIN THE UNITED STATES AND PUERTO RICO

YEAR	MILITARY	CIVILIAN	TOTAL	DEATHS
1965	51	105	156	2
1966	620	144	764	4
1967	2697	159	2856	2
1968	2557	129	2686	6
1969*	3914	145	4059	9
1970*	4088	151	4239	3
1971*	2856	191	3047	8
1972* (through Sep 30)	716	75	791	1

*Gibson J: Personal Communication, 9 January 1973. *For* M.G. Schultz, D.V.M., M.D., Chief, Parasitic Diseases Branch, National Communication Disease Center, Atlanta, Georgia.

Although the military cases of malaria recorded in Table 2 appear to outnumber the civilian cases, Neva et al /5/ pointed out that many of the cases tabulated as military were, in fact, diagnosed and treated in civilian medical facilities. Analyzing mortality data from 1965 through 1969, they calculated a case fatality rate of less than one percent among over 1200 patients with falciparum infections treated in military hospitals. However, for falciparum infections treated in civilian medical facilities, the case fatality rate was a substantial 10 percent.

This review is intended to familiarize all physicians, both military and civilian, with the salient clinical features and ease of laboratory diagnosis of this disease so that cases can be readily diagnosed and appropriately treated early enough to prevent significant morbidity and mortality.

THE SETTING

The diagnosis of malaria should be considered in any patient who is suffering with intermittent high fever and chills and who gives a history of travel in an endemic area. At the present time, such patients fall into two groups. The first, and in recent years the most frequently encountered, is the active duty or recently discharged *serviceman* who has served a tour of duty in Southeast Asia within the previous two years. Included in this endemic area are the Republic of Vietnam, Thailand, Cambodia, Laos, and Korea. When duty in an endemic area has been acknowledged, it should be determined if the patient has been actually "exposed" to malaria.

Exposure usually occurs in jungles, swamps, and small villages. Malaria is rarely contracted in large cities and military base camps with sanitation and mosquito controls. Soldiers have been strongly encouraged to maintain an antimalarial chemoprophylaxis program during their tour of duty and for a short period following return from an endemic area. This consists of a "C-P pill" (chloroquine 500 mg and primaquine 45 mg) given each Monday while in the endemic area. The most recent "out-of-country" follow-up prophylaxis program consists of chloroquine, 1000 mg x one day, primaquine, 26.3 mg/day x 14. Dapsone, one per day x 28, is suggested for those who were taking dapsone daily in prophylaxis against falciparum malaria. Non-compliance with these measures has been highly correlated with the occurence of vivax malaria /6/ and a history of a break in prophylaxis is frequently obtained from patients.*

The second group consists of Peace Corps workers and tourists returning from endemic areas, notably Southeast Asia, South America, and Africa. The same "exposure" history should be obtained as well as a break in chemoprophylaxis (if any). Of particular importance is the identification of the specific endemic area to which the patient was exposed. Chloroquine-resistance to falciparum malaria is rare in Africa but is "the rule" in Southeast Asia.

CLINICAL PRESENTATION

The clinical hallmarks of malaria are intermittent *high* fever and *vigorous* shaking chills alternating with periods of well-being. The symptoms usually last 4-12 hours during which time the patient feels terribly ill; the interludes of well-being last 12-48 hours depending upon the infecting species and relative maturities of parasite populations in the host. Other symptoms, when present, include headache, myalgias, anorexia, and nausea, but these are usually not the prominent features of presentation. Patients may be symptom-free up to two years or more following departure from an endemic area.

Physical examination reveals a remarkable absence of positive findings in the uncomplicated case. Temperature spikes characteristically rise above 104 F, and then drop below 100 F during the symptom-free interlude. Sustained temperature elevation is rare. Infrequently, postural hypotension is demonstrable. Hepatic and splenic tenderness to percussion and splenomegaly may be the only positive findings present.

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* "Breaks" have occurred for a variety of reasons. (1) diarrhea and abdominal cramping, a frequent side-effect of the "C-P pill", (2) non-availability of the drug: and (3) lack of encouragement from superiors.

LABORATORY DIAGNOSIS

Definite diagnosis of malaria is established from recognition of the parasite in the peripheral blood smear from a suspected case. Neither a sophisticated laboratory nor a special staining procedure is necessary. A conscientious physician and a simple "CBC smear" (Wright's stain) suffice in all but rare instances. In cases highly suspect on clinical grounds but with a low degree of parasitemia the physician may need to spend up to an hour examining the smear to find the one or two pathognomic parasites. The thick smear Giemsa's stain may be helpful in these cases.

Species differentiation is *obligatory* since *Plasmodium falciparum* is potentially fatal and its presence must always be ruled out. Moreover, specific treatment for cure is based on species identification. When malaria parasites can be positively seen but species identification is impossible, therapy should not be delayed.

P. vivax and *P. falciparum* account for 99.9 percent of malarias acquired in Southeast Asia. As far as it is known, *P. vivax*, *P. ovale* and *P. malariae* are "definitely not falciparum". The potentially malignant *P. falciparum* must be sought in every case. Mixed *P. vivax* and *P. falciparum* infections are not uncommonly encountered and thus initial recognition of vivax forms requires a further search to rule out concomitant presence of *P. falciparum*. One would not wish to treat a patient for *P. vivax*, only while he runs the risk of dying from *P. falciparum!* Even if a skilled technician has made the species identification, the physician should always verify it because it is on his shoulders that the success orfailure of species-specific treatment rests. Table 3 lists some of the differential features of vivax and falciparum smears.

TABLE 3 [7]

SPECIES IDENTIFICATION

P. falciparum	*P. vivax*
Parasite inhabits cells of all ages	Parasite found primarily in young, immature red blood cells (i.e. those which are larger and/or which exhibit basophilic stippling)
Rings small — could often fit four per red blood cell, frequently demonstrate double chromatin dots; cells often doubly infected	Rings large — could fit at most three per red blood cell, frequently have only single chromatin dot, rarely see doubly infected red blood cells
Trophozoites are rare	Trophozoites are frequent
Gametocytes are the pathognomic "banana" forms	Gametocytes are rare

The first step in correctly interpreting a malaria smear is to recognize artifacts caused by overlying platelets, debris, or drying and staining defects. These artifacts characteristically appear refractile and "shiny" with slight up-and-down focusing movements of the microscope objective, whereas the malaria parasites simply go out of focus.

Species identification is further aided by the use of a picture chart of typical vivax and falciparum forms as they appear in the peripheral blood. Most textbooks of microbiology, parasitology, or tropical medicine have such charts. A particular useful guide is contained in *Manual for Microscopical Diagnosis of Malaria in Man* obtainable from the U.S. Department of Health, Education and Welfare, (Publication No. 796) at a cost of fifty cents.

Th diagnosis of malaria can also be confirmed by serologic studies Antibody response to malaria has been known since 1907 and since 1960 diagnostic serologic methods have become available. The most useful serologic studies are the indirect hemagglutination test (I.H.A.) and the indirect fluorescent antibody test (I.F.A.). Constant titers greater than 1:16 indicate previous infection, while serial four-fold increases indicate active infection. The I.H.A. test is not species specific whereas, the I.F.A. test is and therefore is able to differentiate, for example, *P. falciparum* from *P. vivax*. Peak antibody titers occur from one week to two months following infection. Because of the importance of time in managing malaria, serologic methods have limited immediate clinical value. Serologic studies are useful in epidemiologic research and in evaluating the results of therapy. Immunologic research may ultimately result in the development of a vaccine. Within recent years a protective malaria antibody has been isolated and an antigen capable of stimulating protective antibody has been fractionated. Successful active immunization against malaria in monkeys hopefully heralds an effective human antimalarial vaccine.

THERAPY FOR MALARIA

Prophylaxis for persons in endemic areas is a combination tablet of chloroquine (500 mg) and primaquine (26.3 mg) which is taken once weekly. Upon leaving the endemic area, primaquine (26.3 mg) should be taken daily for fourteen days as well as chloroquine (1000 mg) on the first day. This should be effective suppressive therapy "in country" and curative after leaving the endemic area for *P vivax, P. ovale, P malariae,* and chloroquine-sensitive *P falciparum*

P vivax continues to be the most prevalent form of *acute malaria* in veterans of Vietnam (75-85 percent) Therapy for *P vivax* is given in

Table 4. This is also effective therapy for *P. ovale* and *P. malariae*. The 90-95 percent incidence of resistance of *P falciparum* contracted in Vietname to the chloroquine-primaquine regimen has led to an alternative, three-drug approach to therapy for acute falciparum malaria (Table 4). If the falciparum-infected patient fails to respond to initial therapy with decreasing parasitemia,* *or* if he evidences poor compliance, nephritis, pulmonary edema, or cerebral malaria, *or* if after completion of the initial course of therapy, parasitemia recurs, intravenous administration should replace oral administration of quinine and the entire treatment repeated (Table 4). For the treatment of *mixed infection* (with *P. vivax, ovale* or *malariae)*, primaquine can be added. In the presence of *cerebral malaria* with cerebral edema, corticosteroids may be indicated and, if evidence of disseminated intravascular coagulation is present, heparin may be considered.

If the second course of three-drug therapy for falciparum malaria is followed by recurrence of parasitemia or if increasing parasitemia persists, the criteria are fulfilled for *multidrug resistant malaria* and experimental therapy with trimethoprim and sulfalene or sulfisoxizole or WR33063 is indicated. These drugs can be procured from Walter Reed Army Institute of Research in Washington, D.C.

COMPLICATIONS

The malignant potential of *P. falciparum* is manifested by the multisystem complications it is capable of producing. The pathogenesis of these advanced states of infection is mediated by massive hemolysis, disseminated intravascular coagulopathy, and severe derangement of fluid and electrolytes. These pathologic states are generally correlated with high degrees of parasitemia The systems involved are the central nervous system, cardiopulmonary, and renal.

Daroff et al /8/ reported a 1.6 percent incidence of the various "cerebral syndromes" in their study of 1200 falciparum cases. There were no deaths among these cases (all of whom were treated "expectantly") but their review of mortality of cerebral malaria in previous reported series ranged from 0 to 47 percent. "Cerebral syndromes" include disturbances of consciousness (lethargy and disorientation ranging to frank coma), acute organic brain syndrome, movement disorders, focal neurologic signs, and acute personality changes. Pathogenesis may be explained on the basis of vessel plugging or hemorrhages secondary to disseminated intravascular coagulopathy and cerebral edema. Specific treatment considerations in addition to antimalarials include heparin, low-molecular-weight Dextran ⊙, corticosteroids, anticonvulsants, and blood.

*Parasites may continue to be present in decreasing numbers for three to five days following initiation of treatment.

TABLE 4

GENERAL THERAPEUTIC REGIMENS FOR MALARIAS

DRUG	DOSAGE
For *P. vivax, P. ovale,* and *P. malariae*	
Chloroquine phosphate	1000 mg (600 mg base) p.o. stat 500 mg (300 mg base) p.o. in 6 hours 500 mg (300 mg base) p.o. on day 2 & 3
Primaquine phosphate	26.3 mg (15 mg base) p.o. daily x 14 days
For acute *P. falciparum*	
Quinine sulfate	650 mg p.o. q 8 hours x 10 days
Pyrimethamine	25 mg p.o. q 12 hours x 3 days
Sulfisoxazole (Gantrisin®)	500 mg p.o. q 6 hours x 7 days
For failure to respond; recurrent parasitemia, etc.	
Quinine dihydrochloride	600 mg in 300-400 cc saline intravenously q 8 hours x 14 days
Pyrimethamine	25 mg p.o. q 12 hours x 3 days
Sulfisoxazole	500 mg p.o. q 6 hours x 14 days
For mixed infection, *add concomitantly with regimen for "failure to respond"* . . .	
Primaquine	26.3 mg (15 mg base) p.o. daily x 14 days
For multidrug-resistant malaria*	
Trimethoprim and sulfalene	. . .*
or	
Trimethoprim and sulfisoxazole	. . .*
or	
WR33063	*

*Experimental therapy. Drugs and dosage recommendations can be procured from Walter Reed Army Institute of Research, Washington, D.C.

Cardiac failure may result from severe hemolytic anemia coupled with excess demands engendered by the highly toxic state. A peculiar pulmonary edema accompanied by a low central venous pressure and expanded plasma volume may ensue. Digitalization, improvement of anemia, and careful fluid and electrolyte corrections constitute treatment.

The rare renal complications include hemoglobinuric nephropathy, acute tubular necrosis and acute glomerulonephritis.

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